

Informed Consent in *Safeguarding Children: Pediatric Medical Countermeasure Research*

This is an advanced learning module. Although it covers a topic accessible to most learners—the informed consent process with children, including parental permission and meaningful child assent—it does so specifically in the context of pediatric medical countermeasure research. The ethical analysis in this context is closely tied to complex federal regulations, and some module material might be better suited for more advanced students.

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I. Introduction

In its report, *Safeguarding Children: Pediatric Medical Countermeasure Research*, the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) advised the U.S. government on the ethical considerations involved in evaluating and conducting pediatric medical countermeasure research both before a bioterrorism attack (pre-event) and after an attack (post-event). The Bioethics Commission’s analysis included specific consideration of anthrax vaccine adsorbed (AVA), a vaccine that would be made available for post-event prophylaxis in the event of an anthrax attack.

The term medical countermeasure (MCM) has been defined in different ways. In *Safeguarding Children*, the Bioethics Commission considered it to include U.S. Food and Drug Administration (FDA)-regulated products and interventions used in response to chemical, biological, radiological, and nuclear attacks.¹ Development of pediatric MCMs lags in comparison to MCMs for the adult population in part due to the challenges inherent in collecting relevant dose and immunogenicity data for children.²

There are federal regulations in place to protect human research participants and to guide ethical human subjects research in general. These regulations—referred to as the Common Rule and codified in the Code of Federal Regulations as 45 C.F.R. Part 46, Subpart A—have been adopted by eighteen federal agencies. The federal regulations outlined in 45 C.F.R. Part 46, Subpart D (Subpart D) provide additional protections for research involving children.³ These additional protections are necessary because children cannot ethically or legally consent to participate in research. According to these regulations, permission for children to participate in research must be provided by parents or the appropriate legal guardians and assent to participate generally must be sought from children when they are capable of providing it.⁴

II. Learning Objectives

Students should be able to:

1. Understand and discuss the differences between informed consent with adults and the informed consent process for children to participate in research (i.e., informed parental permission and meaningful child assent).
2. Understand and discuss the ethical underpinnings of informed parental permission and meaningful child assent.
3. Discuss the particular benefits and challenges to ensuring informed parental permission and meaningful child assent in the context of MCM research.
4. Understand the ethical differences between pre-event and post-event pediatric MCM research and how the process of obtaining informed parental permission and meaningful child assent differs between them.

¹ Presidential Commission for the Study of Bioethical Issues (PCSB). (2013, March). *Safeguarding Children: Pediatric Medical Countermeasure Research*. Washington, DC: PCSB, p.18.

² Letter from Secretary Kathleen Sibelius, Health and Human Services (HHS), to Amy Gutmann, Chair, PCSB. (2012, January 6), p. 1. Retrieved June 24, 2014, from <http://bioethics.gov/sites/default/files/news/Pediatric%20Countermeasures%20Letter%20from%20the%20Secretary.pdf>.

³ The FDA has also adopted substantively identical regulations which can be found in *Protection of Human Subjects, FDA*. 21 C.F.R. Part 50, Subpart D.

⁴ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.408.

III. Background

In *Safeguarding Children*, the Bioethics Commission examined the history and implementation of pediatric research protections generally in addition to scrutinizing pediatric research protections as they relate to MCM research specifically, and made recommendations concerning the ethical conduct of pre- and post-event MCM research with pediatric populations. Pre-event research is conducted in advance of an attack in which an MCM might be needed, and post-event research takes place after an attack has occurred, when an MCM might already be available to affected individuals. The Bioethics Commission also discussed the informed consent process and how it differs in pediatric research from research with adult participants.

A. Informed Consent Process with Children

The Common Rule establishes general requirements for informed consent with adults including, but not limited to, explanation of the research study, description of expected benefits and potential risks, explanation of confidentiality, description of available medical care and compensation for research related injury, and a statement of voluntariness specifying that participants can withdraw from the study at any time with no penalty.⁵ In addition to these requirements, additional protections are in place for the informed consent process for research involving children.

Subpart D outlines stringent protections for child research participants.⁶ It provides that, generally, “children cannot participate in research that poses higher risks than those of daily life, except in circumstances where research offers the prospect of benefit to participants themselves or to those with the same condition.”⁷ By contrast, adults can consent to participate in research from which they will accrue no direct benefit for themselves but that might benefit others, without similar risk-level limitations.⁸ The impetus for specialized regulatory protection for children involved in research stems from the recognition that children have increased vulnerability and cannot ethically or legally consent to assume research risks. Children as a class are vulnerable for multiple reasons including expectations of “deference to adult authority, lack of independent resources for autonomous decision making, and longstanding institutionalized relationships of adult authority and power.”⁹

Children ethically and legally cannot give autonomous informed consent to participate in research because their autonomy forms over time and is not fully developed until adulthood. The moral and legal equivalent of informed consent in pediatric research involves two components: informed parental permission and meaningful child assent. Parental permission requires parents

⁵ *Protection of Human Subjects*, HHS. 45 C.F.R. §46.116.

⁶ *Protection of Human Subjects*, HHS. 45 C.F.R. Part 46, Subpart D.

⁷ PCSBI, (2013, March), *op cit*, p. 37.

⁸ *Ibid*, p. 37.

⁹ *Ibid*, p. 26.

to act on their child's behalf and in their child's best or essential interests.¹⁰ It is important to note, however, that parental permission generally cannot override a child's sustained and meaningful dissent.¹¹

Child assent is important and should be sought in addition to parental permission, but assent must not be interpreted as a substitute for parental permission.¹² Seeking meaningful child assent (or meaningful dissent) demonstrates respect for children's developing autonomy and their ability to make informed, self-regarding choices about how they will be treated.

In order for assent to be meaningful, children must understand to the best of their developmental abilities the procedures involved in the research protocol, voluntarily choose to participate, and communicate their choice to do so.¹³ Meaningful child dissent is the opposite, in which children demonstrate developmentally appropriate understanding of research participation and communicate a desire and choice not to participate. Assent and dissent must be meaningful in the context of the child's maturity. For example, an infant's cries when receiving a shot do not demonstrate meaningful dissent.

Obtaining parental permission, and meaningful child assent if possible, is essential for ethical research involving child participants, but is particularly important in pre-event MCM research as participants have no prospect of direct benefit from participation. By definition, MCMs are used in response to a chemical, biological, radiological, or nuclear attack, so no children would benefit from MCM research in the absence of an attack; potential benefits could only accrue to children as a group in the future. In post-event research, when an MCM is administered after an attack, participants might receive a direct benefit from the research (e.g., monitoring and mitigating any adverse events), the research might benefit children who have the same condition, or the research might pose only minimal risk. Informed parental permission and child assent are as important in this context as in pre-event MCM research, although the process of obtaining permission might be made more challenging by the emergency circumstances in which post-event research takes place. In *Safeguarding Children*, the Bioethics Commission emphasized the central importance of informed parental permission and meaningful child assent in all pediatric MCM research, whether that research takes place before or after an attack.

¹⁰ This module refers to parental permission throughout, and in all cases this should be understood to include permission given by legal guardians as well as by parents.

¹¹ There are two possible exceptions to requiring participant assent, as outlined in 45 C.F.R. § 46.408(a). (1) when the research offers a prospect of direct benefit to participants that is otherwise unattainable with existing alternatives; and (2) when, taking into account the age, maturity, and psychological state of potential participants, an institutional review board (IRB) determines that participants are not competent to reasonably be consulted. In addition, the IRB could waive the assent requirement under circumstances in which consent may be waived under 45 C.F.R. §46.116 (General requirements of informed consent).

¹² PCSBI, (2013, March), op cit, p. 27.

¹³ Rossi, W.C., Reynolds, W., and R.M. Nelson. (2003). Child assent and parental permission in pediatric research. *Theoretical Medicine and Bioethics*, 24(2), 131-148.

B. Guiding Ethical Principles

Pediatric research is ethically complex because children ethically and legally cannot consent to participate. Children's partial autonomy and vulnerability establish the need for stringent research protections including limits on the types of risk children should be asked to incur in research.

In forming its recommendations, the Bioethics Commission drew on previous work by national bioethics commissions establishing ethical principles for pediatric research and human subjects research more generally. In its 1977 report, *Research Involving Children*, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission) made recommendations for pediatric research embodying ethical principles that were then set forth more broadly in the National Commission's 1978 *Belmont Report*. These principles include respect for persons, beneficence and its corollary non-maleficence, and justice.¹⁴ The Bioethics Commission also identified democratic deliberation, implicit in the National Commission's work, as integral to ethical conduct of research with children. Of these principles, respect for persons and beneficence are especially relevant to informed consent.

Respect for persons acknowledges individuals' autonomy and ability to consider personal goals, choices, and opinions in deciding how to live their lives, and supports the concept that those with diminished autonomy (including children) are entitled to enhanced protections. This principle requires that fully autonomous research participants be informed about and have the opportunity to give consent to participate in research. Since children lack the capability to give ethically and legally valid consent to participate, demonstrating respect for persons with child research participants requires obtaining fully informed parental permission and meaningful child assent.

Some scholars consider the obligation of protection to be a matter of beneficence.¹⁵ Beneficence is the obligation to undertake efforts to secure the wellbeing of others.¹⁶ This obligation is especially salient in pediatric research due to children's reduced autonomy and inability to

¹⁴ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1977). *Research Involving Children: Report and Recommendations*. (DHEW Publication OS 77-0004). Washington, DC: Department of Health, Education, and Welfare; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. (DHEW Publication OS 78-0012). Washington, DC: Department of Health, Education, and Welfare.

¹⁵ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. (DHEW Publication OS 78-0012). Washington, DC: Department of Health, Education, and Welfare; Beauchamp, T.L. (2005). The Origins and Evolution of the Belmont Report. In J.F. Childress, E.M. Meslin, and H.T. Shapiro. (Eds.). *Belmont Revisited: Ethical Principles for Research with Human Subjects*. Washington, DC: Georgetown University Press, pp. 15-16. For a similar debate on of the relationship between autonomy and beneficence regarding pediatric research, see Miller, R.B. (2003). Ethical Issues in Pediatric Research. In *Children, Ethics, and Modern Medicine*. Bloomington, IN: Indiana University Press; Ramsey, P. (1970). *The Patient as Person*. New Haven, CT: Yale University Press.

¹⁶ PCSBI (2013, March), op cit. p. 30.

ethically and legally consent to participate in the research. Beneficence supports both the requirement for parental permission and meaningful child assent and limiting the level of risk that can be incurred. These measures protect individual children involved in research. Importantly, beneficence also applies to society as a whole—including children as a class—encouraging the conduct of ethical research that might benefit children in the future.

C. Bioethics Commission Recommendations

In its discussion about the importance of informed parental permission and meaningful child assent in pediatric MCM research, the Bioethics Commission stated that “the process of seeking parental permission and meaningful child assent in pre-event pediatric MCM research should be conducted by an independent person with expertise in developmentally appropriate child assent procedures. While an assent monitor is advisable in minimal risk pediatric MCM research, the employment of an independent person to obtain consent is imperative in pediatric MCM research that involves greater than minimal risk and no prospect of direct benefit.”¹⁷

Three of the report’s six recommendations emphasize parental permission and meaningful child assent. Recommendation 4 applies to pre-event pediatric MCM research when the potential risks are greater than minimal:

Recommendation 4: Ethical Framework for National-Level Review of Pre-event Pediatric Medical Countermeasure Research *[excerpt]*

To ensure the thoroughness and ethical rigor of national-level review, reviewers should apply the Bioethics Commission’s recommended ethical framework for reviewing pre-event pediatric medical countermeasure research that poses greater than minimal risk, but no more than a minor increase over minimal risk, under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug Administration regulations at 21 C.F.R. § 50.54. A proposed protocol must meet the requirements of the framework outlined in this report to be approved.

The framework clarifies the circumstances in which proposed research presents a “reasonable opportunity” to address a “serious problem,” in particular, that seriousness must be judged by the consequences of exposure, likelihood (or threat) of exposure, and the “vital importance” of the information to be gained.... [T]he framework reiterates the importance of informed parental permission and meaningful and developmentally appropriate child assent.¹⁸

The necessary information conveyed through the informed consent process can be technical and difficult to communicate to parents and potential child participants. The Bioethics Commission acknowledged the complexity inherent in MCM research and suggested that “one means of

¹⁷ PCSBI, (2013, March), op cit, p. 85.

¹⁸ Ibid, p. 87.

ensuring that all the relevant information is clearly conveyed could be to present a video about the research to the participants and their parents, followed by an opportunity to ask questions.”¹⁹

Recommendation 5 addresses parental permission and child assent in post-event pediatric MCM research:

Recommendation 5: Post-event Pediatric Medical Countermeasure Research

Post-event research should be planned in advance and conducted when untested medical countermeasures are administered to children in an emergency or when limited pre-event medical countermeasure studies have already occurred. Institutional review boards must be cognizant of the exigencies imposed upon research under emergency conditions, and when reviewing post-event medical countermeasure research proposals, ensure that adequate processes are in place for informed parental permission and meaningful child assent. Institutional review boards must also ensure that the research design is scientifically sound, children enrolled in research have access to the best available care, adequate plans are in place to treat or compensate children injured by research, and provisions are made to engage communities throughout the course of research.²⁰

The Bioethics Commission acknowledged that the process of obtaining informed parental permission and meaningful child assent might be strained under emergency circumstances following a bioterrorism event, and stressed the importance of efforts to adequately inform parents so that they might make a reasoned decision about whether to participate in research. For example, consent forms and information should be as simple and straightforward as possible while still including the essential information required for an informed decision.²¹

The Bioethics Commission considered a situation in which the government has no MCM available that has been approved by FDA. In this situation FDA can authorize the use of the MCM under an emergency use application (EUA) if data exist from pre-event testing of the drug. Under an EUA the drug can be distributed via a streamlined informed consent process on the basis of the existing data and the need for timely provision of MCMs in an emergency.²² The Bioethics Commission found that when there are no pediatric data from pre-event testing, the distribution of an MCM to children should be authorized under an investigational new drug application (IND), in which all human subjects research protections apply, including institutional review board (IRB) review and documented informed permission from parents or guardians.²³ Children could receive the MCM under a *treatment IND*, and an *investigator IND* would allow

¹⁹ PCSBI, (2013, March), op cit, p. 85.

²⁰ Ibid, p. 97.

²¹ Ibid, p. 92.

²² Ibid, p. 99.

²³ National Biodefense Science Board. (2011). *Challenges in the Use of Anthrax Vaccine Adsorbed (AVA) in the Pediatric Population as a Component of Post-Exposure Prophylaxis (PEP): A Report of the National Biodefense Science Board*. Retrieved June 24, 2014, from <http://www.phe.gov/Preparedness/legal/boards/nprsb/recommendations/Documents/avwgrpt1103.pdf>, p.34.

researchers to obtain more detailed public health surveillance data from a subset of children who receive the intervention. Both the treatment and the investigator IND require a thorough informed process of parental permission and child assent.²⁴

Recommendation 6 addresses parental permission and child assent for the post-event distribution of an unapproved MCM. Importantly, in a post-event situation, MCMs would generally be available to exposed individuals, including children. In this circumstance, MCM research might be considered minimal risk (e.g., limited to observational procedures), offer the prospect of direct benefit to participants due to their exposure to the bioterror agent, or yield information of vital importance to understanding or ameliorating the condition resulting from exposure.²⁵

Recommendation 6: Regulatory Mechanisms for Post-event Pediatric Medical Countermeasure Research and Distribution

When there are no data on the administration of a medical countermeasure to children and it will be provided to children in an emergency, the medical countermeasure should be provided under a treatment investigational new drug application (IND) to ensure that rigorous pediatric research protections apply to safeguard those children who receive the medical countermeasure. When a medical countermeasure is distributed broadly to children using a treatment IND, it is essential that the U.S. government also conduct a concurrent small-scale study under an investigator IND to obtain data that can potentially be used to support an emergency use authorization for pediatric use of the medical countermeasure in a future event. To expedite post-event research and ensure the availability of appropriate medical countermeasures for children, a pre-IND consultation and approval should be put in place before an event.²⁶

IV. Reading

For the purposes of discussion, students should download and read the following Bioethics Commission materials (reports are available for download on the Bioethics Commission's website at www.bioethics.gov under "Projects").

Safeguarding Children: Pediatric Medical Countermeasure Research, pp. 24-30
("Respect for Persons").

Safeguarding Children, pp. 82-86 ("Are Adequate Provisions Made for Soliciting the Permission of Parents or Guardians and the Meaningful Assent of Children?").

Safeguarding Children, pp. 90-92 ("Ethical Issues in Post-event Research").

²⁴ PCSBI, (2013, March), op cit, p. 103.

²⁵ Ibid, p. 89.

²⁶ Ibid, pp. 101-102.

V. Discussion Questions

The following questions are based on the information provided above and through the indicated reading and are intended to reinforce important aspects of informed parental permission and meaningful child assent that are highlighted in the Bioethics Commission's *Safeguarding Children* report. Important points are noted with each question to help the instructor guide a group discussion. The "Additional Resources" section will be helpful in answering these questions.

- 1. One of the challenges in adequately providing for informed parental permission and meaningful child assent is providing age-appropriate materials to convey information about the research to pediatric research participants. How does this challenge differ based on the age of the child? How might it be resolved?**

Starting points for discussion:

- a. Example challenge: For young children (e.g., elementary school-aged) it can be difficult both to convey complex concepts and to ascertain willingness to participate.

Example resolution: Illustrations and simple explanations could be used to describe the child's experience of participating in research.

- b. Example challenge: When children are nearing the age of legal consent they might be able to understand, question, and discuss information regarding research participation. How can their developing autonomy be respected?

Example resolution: Children and parents should each receive appropriate information about a study and be individually engaged in a discussion regarding permission and assent.

- 2. Obtaining children's developmentally appropriate and meaningful assent can be logistically challenging, but doing so properly is an ethical imperative. Explain why.**

Starting points for discussion:

- a. Informed consent, or its moral equivalent, is an important mechanism for respecting persons. It is a stringent requirement in research involving human participants, regardless of age, developmental stage, or other factors.
- b. Informed consent—and in the case of research involving children, parental permission and meaningful child assent—is an articulation of the principle of respect for persons, which recognizes persons as autonomous and capable of

deliberating about their personal goals, considering their own choices and opinions, and determining the course of their own lives.²⁷ Respect for persons extends to individuals with developing or diminished autonomy, including children.

VI. Problem-Based Learning

Scenario A. *A parent sees an advertisement for medical countermeasure research, specifically, for a treatment for an emerging biological threat. She values research and considers involving her school-aged child in the study. She brings her child to a pre-screening appointment with the research team and they begin the informed consent process. The researcher explains to the parent that the project involves a series of blood draws. The researcher also explains this to the child. As soon as the child hears about the blood draws, he asks if a needle is involved and states that he “will not let anyone stab him with a needle.” He begins to exhibit physical signs of distress as the conversation continues. The mother gives permission, but the child ceases participating in the discussion.*

1. How could the researcher handle this situation?

Starting points for discussion:

- a. The researcher can consider whether the child’s actions should be considered meaningful dissent (this will depend in part on the child’s age and developmental stage).
- b. The researcher should not enroll the child in the research if his dissent is meaningful and sustained—e.g., if the child continues to be unwilling to participate after talking further with the researcher or watching an age-appropriate video about the study.

2. What challenges might arise for a parent giving permission for their child to participate in pre-event MCM research, like the study in this scenario? What different challenges might arise when giving permission for post-event MCM research?

Starting points for discussion:

- a. For pre-event MCM research challenges might include:

²⁷ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research*. (DHEW Publication OS 78-0012). Washington, DC: Department of Health, Education, and Welfare.

- i. Comprehension of complex concepts, for example, the unknown and unknowable likelihood of a bioterrorism event occurring; and research that will produce results that we hope never to use.
 - ii. Parents might misattribute participation in the research as a means of ensuring their child's safety in the event of an attack. The researcher would need to clarify the degree to which participation in the study might result in increased protection for the child, if any.
- b. For post-event MCM research challenges might include:
 - i. The stress of post-event circumstances and the difficulty of effective communication between researchers and parents about the research and why it is necessary, in the midst of an emergency;
 - ii. The possibility that parents and children are in different locations, making it difficult for parents to document their permission for children either to receive the MCM or to participate in post-event public health surveillance or research; and
 - iii. The possibility that parents might conflate participating in the research with treatment.

Scenario B. *Following a suspected anthrax attack at a federal facility, exposed individuals, including children, are to be given prophylaxis in the form of a vaccine, and antibiotics. The vaccine has been tested on adults but not on children, so health officials plan to give the vaccine to the children under a treatment IND, and to conduct post-event research on a subset of those children under an investigational IND, to obtain immunogenicity and active surveillance data.*

You can read more about treatment and investigator INDs here:

Safeguarding Children, pp. 97-102 ("Authorizing Distribution of Unapproved Drugs in an Emergency").

Safeguarding Children, pp. 102-105 ("Application to Post-event Trials of AVA with children").

National Biodefense Science Board. (2011). *Challenges in the Use of Anthrax Vaccine Adsorbed (AVA) in the Pediatric Population as a Component of Post-Exposure Prophylaxis (PEP): A Report of the National Biodefense Science Board*. Retrieved June 24, 2014, from:

<http://www.phe.gov/Preparedness/legal/boards/nprsb/recommendations/Documents/avwgrpt1103.pdf>.

1. What are the advantages and disadvantages of giving the MCM to children under an IND?

- a. Advantages:
 - i. Under a treatment IND all pediatric research protections apply to the distribution of the vaccine, including IRB review and documented parental permission.
 - ii. An investigator IND allows researchers to obtain more detailed surveillance data from a subset of children who receive the intervention.
- b. Disadvantages:
 - i. An IND requires documented parental permission, which could be difficult to obtain if parents are not in the same location as their children.
 - ii. Parents and children might receive the intervention with different consent processes if the vaccine is given to adults under an EUA.

2. Some children who receive the MCM will be monitored in post-event research to study the safety and effectiveness of the intervention. What challenges might researchers encounter in obtaining consent for this research?

- a. Time might be limited, making it difficult to have lengthy information discussions with parents and potential child participants;
- b. Parents and children might be stressed and anxious, making it difficult to present information effectively and obtain informed parental permission and meaningful child assent.

VII. Informed Consent Exercises

Exercise 1. *Find an example of a parental permission document for pediatric research and answer the following questions. Documents for various protocols might be found on the websites of research hospitals, universities, the National Institutes of Health, and other organizations. Templates or examples of parental permission documents will suffice for this exercise.*

The following additional resource might be helpful in answering these questions:

Klein, N., Research Scientist II, Kaiser Permanente Northern California Division of Research, Co-Director, Kaiser Permanente Vaccine Study Center. (2012). Presentation to

the Bioethics Commission, May 17. Retrieved June 24, 2014 from
<http://bioethics.gov/node/709>.

1. For what age group is this document designed?

- a. How can you tell this document is designed for that particular age group?
- b. How might this document be re-designed for different age groups? For example, a 5-7 year-old age group, or a 15-18 year-old age group?
- c. Would the document need to be re-written for different age groups?
- d. How could the document be more age-appropriate?
- e. What concepts about participation in research are most difficult to convey for a younger participant?

2. What other material might be used to facilitate the parental permission and child assent process?

Exercise 2. *Design an informed consent process for a pre-event MCM study with adolescents 15-17 years of age. The study involves a minor increase over minimal risk, and will test an MCM that previously has been tested with adults to determine safe dosage levels.*

The following additional resource might be helpful in answering these questions:

Klein, N., Research Scientist II, Kaiser Permanente Northern California Division of Research, Co-Director, Kaiser Permanente Vaccine Study Center. (2012). Presentation to the Bioethics Commission, May 17. Retrieved June 24, 2014 from
<http://bioethics.gov/node/709>.

1. What materials might be developed for the informed consent process?

- a. Materials might include: permission forms for parents, age appropriate assent forms, informational brochures or other means of conveying information, scripts for communicating with parents and children, and informational videos.

2. What information is conveyed to both parents and children?

- a. The information provided should be in compliance with federal regulations, specifically 45 C.F.R. Part 46, and should include: information regarding the research plan, the potential benefits and risks associated with participation, acknowledgement of the ability to withdraw from the research at any time without penalty, and what to expect regarding privacy.

- b. The same information should be communicated to both parents and children, but in an age appropriate manner for the adolescents.
- c. Researchers should explain the relevance of prior testing of the intervention with adults, and the lack of any prior testing with children.
- d. Researchers should discuss with participants the fact that participating in the research does not pose a prospect of direct benefit to the participants.

VIII. Glossary of Terms

Anthrax vaccine adsorbed (AVA): An FDA-licensed human anthrax vaccine approved for pre-exposure use in those 18-65 years of age who are at high risk of exposure to anthrax.

Autonomy: The capacity to direct the course of one's own life or to live according to one's own values and beliefs.

Beneficence: An obligation on the part of researchers to undertake efforts to maximize possible benefits and minimize potential harms that might impact research participants.

Democratic deliberation: An approach to collective and collaborative decision making that seeks to clarify and articulate factual and ethical issues at the core of a debate, to create consensus whenever possible, and to map the terrain of disagreements in a respectful way—when agreement is not immediately attainable—by encouraging reciprocity, respect for persons, transparency, publicity, and accountability.

Distributive justice: An ethical principle that calls for equitable distribution of benefits and burdens across society—for example, the benefits and burdens of biomedical research, or of technological advances.

Emergency use authorization (EUA): An authorization issued by FDA to allow either the use of an unapproved medical product or an unapproved use of an approved medical product during a declared emergency.

Institutional review board (IRB): A specially constituted review body established or designated by an entity to protect the welfare of individuals recruited to participate in biomedical or behavioral research. The duties and responsibilities of IRBs are described in federal regulations.

Investigational new drug application (IND): An application submitted to FDA before studying a drug or biologic in humans.

An *investigator IND* (used most commonly in research involving interventions) is submitted by a researcher who initiates and conducts an investigation of the investigational new drug.

A *treatment IND* allows for the use of a promising experimental drug in the treatment of patients not enrolled in a clinical trial while the final clinical work and FDA review take place.

Meaningful child assent: Developmentally appropriate agreement to participate in research. Obtaining meaningful assent is one component of respecting the child as a person.

Meaningful child dissent: Developmentally appropriate refusal to participate in research.

Medical countermeasure (MCM): FDA-regulated products and interventions used in response to chemical, biological, radiological, and nuclear attacks.

Minimal risk: Defined by the Code of Federal Regulations as “the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons” (45 C.F.R. §46.303), and generally understood to mean the degree of risk encountered in the daily life of a healthy individual living in a safe environment or the risk to which a healthy individual is exposed during a routine examination.

Minor increase over minimal risk: A level of risk that is a narrow expansion over minimal risk, but entailing no significant threat to an individual’s health or wellbeing.

Parental permission: Permission for a child to participate in research, given by the parent(s) or legal guardian(s) acting on their child’s behalf, operating on their understanding of what is in the child’s best or essential interests.

Respect for persons: Ethical principle requiring that individuals are treated as independent and self-determining (autonomous) agents and that persons with diminished autonomy are entitled to additional protections.

IX. Additional Resources

Berg, J., and N. King. (2006). Strange bedfellows? Reflections on bioethics’ role in disaster response planning. *American Journal of Bioethics*, 6(5), 3-5.

Burns, J.P. (2003). Research in Children. *Critical Care Medicine*, 31(3), S131-S136.

Klein, N., Research Scientist II, Kaiser Permanente Northern California Division of Research, Co-Director, Kaiser Permanente Vaccine Study Center. (2012). Presentation to the Bioethics Commission, May 17. Retrieved June 24, 2014, from <http://bioethics.gov/node/709>.

Kodish, E. (2003). Informed consent for pediatric research: Is it really possible? *Journal of Pediatrics*, 142(2), 89-90.

National Biodefense Science Board. (2011). *Challenges in the Use of Anthrax Vaccine Adsorbed (AVA) in the Pediatric Population as a Component of Post-Exposure Prophylaxis (PEP): A Report of the National Biodefense Science Board*. Retrieved June 24, 2014, from <http://www.phe.gov/Preparedness/legal/boards/nbsb/recommendations/Documents/avwgrpt1103.pdf>.

Rossi, W.C., Reynolds, W., and R.M. Nelson. (2003). Child assent and parental permission in pediatric research. *Theoretical Medicine and Bioethics*, 24(2), 131-148.

Simon, C., et al. (2006). Altruistic discourse in the informed consent process for childhood cancer clinical trials. *American Journal of Bioethics*, 6(5), 40-47.

Ungar, D., Joffe, S., and E. Kodish. (2006). Children are not small adults: Documentation of assent for research involving children. *Journal of Pediatrics*, 149(1), 3-33.